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| 10/551,569      | 10/13/2006  | Christopher McGuigan | 05794.00002         | 3842             |

29880 7590 05/11/2009

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| EXAMINER |
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MOORE, SUSANNA

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| ART UNIT | PAPER NUMBER |
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1624

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05/11/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

|                              |                                      |  |  |
|------------------------------|--------------------------------------|--|--|
| <b>Office Action Summary</b> | <b>Application No.</b><br>10/551,569 | <b>Applicant(s)</b><br>MCGUIGAN ET AL. |  |
|                              | <b>Examiner</b><br>SUSANNA MOORE     | <b>Art Unit</b><br>1624                |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 09 February 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) 16 and 18-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-15, 17 and 22-25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of Group I in the reply filed on 2/9/2009 is acknowledged. Group I, drawn to furano[2,3-d]pyrimidines, simple compositions and a process of making simple compositions thereof, embraced by claims 1-15, 17, and 22-25 was elected by Applicant. Applicant asserts, "that the examination of Groups I to V would not place a serious burden on the Examiner. In order to properly restrict claims there must be an undue burden on the Examiner if the restriction was not made. Group I-V encompass compounds of formula (I). Because all of the claims are related to the same formula (I), Applicants submit that the examination of Groups I to V places no undue burden on the Examiner, as search with the formula (I) will reveal all art related to the structure, function, method of preparing and use of the compounds of formula (I)." This is not found persuasive because according to MPEP §803 "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02. That *prima facie* showing may be rebutted by appropriate showings or evidence by the applicant." Applicant has not pointed to any errors in the Examiner's analysis of the classification of the different inventions. The requirement is still deemed proper and is therefore made **FINAL**.

There are 25 claims pending and 20 under consideration. Claims 1-15, 17, 22 and 23 are compound claims. Claim 24 is a composition claim and claim 25 is a method of preparing said composition. Claims 16 and 18-21 are method of using claims, which are nonelected subject

matter. This is the first action on the merits. The application concerns some furano[2,3-d]pyrimidine compounds, compositions, synthesis, and uses thereof.

### ***Specification***

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Substituted Furano[2,3-d]pyrimidines as a Treatment of Viral Infections.

### ***Claim Objections***

Claims 17, 22 and 23 are objected to because of the following informalities: claims 17, 22 and 23 are substantial duplicates of claim 1 as the only difference is a statement of intended use, which is not given material weight. Note *In re Tuominen* 213 USPQ 89. Appropriate correction is required.

Claim 15 is objected to because of the following informalities: the 4<sup>th</sup> and 8<sup>th</sup> species listed on page 6 of the claims are misspelled. Appropriate correction is required.

Claim 15 is objected to because of the following informalities: a comma is needed after the name of each specie. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14, 17 and 22-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The word “derivatives” in claim 1 is vague. A derivative is a substance or compound obtained from, or regarded as derived from, another substance or compound. What are these “derivatives?” Are the “derivatives” covered by the scope of the genus of formula (I)? Claims which depend from claim 1 which fail to remedy the deficiency of claim 1 are also rejected for the reasons set forth herein.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 3, 5, 7-10 and 13 recite the broad

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recitation “preferably”, and the claim also recites “more preferably” which is the narrower statement of the range/limitation.

Claim 15 is vague. All of the species listed in said claim has numbers after the nomenclature. What are these numbers? Do the numbers refer to the Specification? Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claims 7 and 8 are vague because of the term "C<sub>5-14</sub>aryl." There cannot be a C<sub>5</sub>aryl. Thus, said claims are vague.

Claims 1-14, 17 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. “The [eight] factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims”, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is found in lines 14-16, page 20. c) There is no working example of a prodrug of a compound the formula (I). d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) in the first sentence, third paragraph on page 596 states that “extensive development must be undertaken” to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would

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have a Ph. D. degree and several years of industrial experience. g) It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved”, and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim 1 as well as the presently unknown list potential prodrug derivatives embraced by claim 1.

MPEP 2164.01(a) states, “[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug. The Examiner suggests deleting the term "prodrugs" from claim 1.

**Claim 23 is drawn to a method of treatment of cytomegalovirus viral infection, for which the instant Application is enabled.**

Claims 17 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such a utility cannot be deemed enabled.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one

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considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Some experimentation is not fatal; the issue is whether the amount of experimentation is “undue”; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

**The analysis is as follows:**

**(A) Breadth of claims.**

**(a) Scope of the compounds.** The instant claims encompass millions of compounds with a furano[2,3-d]pyrimidine scaffold with a variety of substituents at five different positions.

**(b) Scope of the diseases covered.** The instant claims are drawn to a method of treatment and a method of treating viral infections. The scope is not known based on claim 17, which is drawn to a method of treatment, generally.

The scope of claim 22, for use in the prophylaxis or treatment of a viral infection, is broad because viral infections are any infection caused by a virus. Some examples of viral infections are, but not limited to: common cold, cold sores, AIDS, chickenpox, Ebola, SARS, AIDS Related Complex, cytomegalovirus infection, Colorado tick fever, Dengue fever, hand, foot and mouth disease, hepatitis, herpes simplex II, herpes zoster, human papillomavirus (HPV), influenza (flu), Lassa fever, measles, Marburg haemorrhagic fever, infectious mononucleosis, mumps, poliomyelitis, progressive multifocal leukoencephalopathy, rabies rubella -smallpox (variola), viral encephalitis, viral gastroenteritis, viral meningitis, viral pneumonia, West Nile

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disease and Yellow fever.

**(B) The nature of the invention and predictability in the art:** The invention is directed toward medicine and is therefore physiological in nature. It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved,” and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

**(C) Direction or Guidance:** That provided is very limited. The dosage range information, found on page 13 of the Specification gives 5-10 mg for a medicament. Moreover, the dosage is generic, the same for the many disorders covered by the Specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for any and all treatments or the treatment of all viral infections.

**(D) State of the Prior Art:** These compounds are furano[2,3-d]pyrimidine scaffold with a particular substitution at five different positions. So far as the examiner is aware, no substituted furano[2,3-d]pyrimidines of this kind have been used for a method of treatment generally or the treatment of all viral infections.

**(E) Working Examples:** The invention is drawn to a method of treatment generally or a method of treating viral infections. On pages 47-50 of the Specification there is one *in vitro* assays completed with CMV-AD169 and CMV Davis. No standard assays were conducted for anti-viral

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activity in the form of *in vivo* or a mammal model.

**(F) Skill of those in the art:** The viral infections listed under Scope of diseases above cannot be treated generally by any one drug. These are all different viral infections, which occur at different locations in the body and by different viruses. Gardasil®, a vaccine which is currently marketed to prevent HPV, only protects against HPV strains 16, 11, 18 and 6, which is the majority of the strains which cause cervical cancer, but is not all the strains.

The great majority of these viral infections have no treatment at all, and of those that do, none have been treated with such G protein heterotrimer formation inhibitors as are disclosed here. The great diversity of viruses falling within the Scope means that it is contrary to medical understanding that any agent (let alone a genus of millions of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. Further, what little success there has been does not point in this direction. Thus, what very few treatments that the massive research effort on virus infections has produced are means of providing vaccines, unrelated to the mechanism of action in this case.

Furthermore, despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for a method of treatment or viral infections, **generally**. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609.

**(G) The quantity of experimentation needed:** Owing especially to factors A, C, E and F, the

amount of experimentation is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

**Claim 23 is drawn to a cytomegalovirus for which the instant Application is enabled.**

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

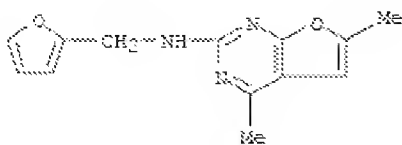
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Bisagni et. al. (Bulletin de la Societe Chimique de France, 1996, 3, page 803-811).

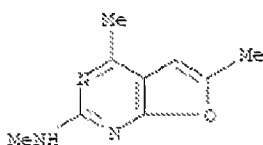
The reference teaches a compound of formula (I), wherein Y= nitrogen, Z= oxygen, U= CR<sup>2</sup>, R<sup>2</sup>= hydrogen, R<sup>1</sup>= methyl, V= CR<sup>3</sup>, R<sup>3</sup>= methyl, X= nitrogen, Q= NH and R<sup>4</sup>= methyl. Another specie is the compound of formula (I), wherein Y= nitrogen, Z= oxygen, U= CR<sup>2</sup>, R<sup>2</sup>= hydrogen, R<sup>1</sup>= methyl, V= CR<sup>3</sup>, R<sup>3</sup>= methyl, X= nitrogen, Q= NH and R<sup>4</sup>= CH<sub>2</sub>furanyl. See compound 28, page 804.

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RN 22727-45-3 CAPLUS  
CN Furo[2,3-d]pyrimidin-2-amine, N-(2-furanylmethyl)-4,6-dimethyl- (CA INDEX NAME)



RN 23691-34-1 CAPLUS  
CN Furo[2,3-d]pyrimidin-2-amine, N,4,6-trimethyl- (CA INDEX NAME)



Thus, said claims are rendered anticipated by Bisagni et.al.

### *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSANNA MOORE whose telephone number is (571)272-9046. The examiner can normally be reached on M-F 8:00-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Susanna Moore/  
Examiner, Art Unit 1624